REMARKS

Claim 8 has been amended to clarify the claim language. Support for the amendment is found in the specification, for example at page 2, line 30 to page 3, line 13; page 58, lines 28-30; page 68, lines 21-29; and the claims as filed. As described in the specification, monitoring includes assaying a sample once or more than once.

No new matter has been added.

Rejection Under 35 U.S.C. 112, First Paragraph

The Examiner rejected claims 1, 6-8, 10 and 37-48 under 35 U.S.C. 112, first paragraph as not enabled. The Examiner indicated that the claims remain rejected for the use of the term "increased relative to a predetermined value" of Fit-1/ST2 in diagnosis and determination of the stage of cardiovascular disease.

The Examiner asserts that the claimed diagnostic methods would be unpredictable due to taking a single Fit-1/ST2 measurement; presumably this applies to claim 1 and its dependent claims. The Examiner also indicated that the specification does not teach how to correlate Fit-1/ST2 levels to regression, progression or onset of cardiovascular disease; presumably this applies to claim 8 and its dependent claim. Finally, the Examiner indicated that the claims are broad enough to encompass diagnosis by comparing measured values of Fit-1/ST2 to a predetermined value that is greater than zero.

Applicant has amended claim 8 and respectfully requests reconsideration of the rejection.

With respect to claim 1 and its dependent claims, Applicant asserts that the specification provides sufficient guidance, in combination with the knowledge of the person of skill in the art, to enable the claimed invention. Applicant notes that specific guidance on this aspect of the invention

was provided in the specification. The passages at page 28, lines 15-32 and page 68, lines 20-29 of the application provide sufficient guidance for the person of ordinary skill in the art of clinical assays to practice the claimed invention.

Moreover, it is entirely routine for persons of ordinary skill in the art of clinical assays to determine a suitable predetermined value that is diagnostic of a condition, such as a cardiovascular condition as claimed herein. To Applicant's knowledge, many if not all clinical assays utilize predetermined values to provide diagnostic information. The operator of the assay measures the value of a parameter (such as Fit-1/ST2 levels as claimed herein) and then compares the measured value to the predetermined value to determine if the value is greater or less than the predetermined value. This comparison provides the diagnostic readout of the assay.

For example, Zebrack et al. (Am J Cardiol 2002;89:145–149) compared CRP levels, measured using a high sensitivity CRP assay, for several cardiovascular conditions (stable (SAP) and unstable angina pectoris (UAP) and acute myocardial infarction(AMI)) as a predictive marker for clinical outcomes of acute myocardial infarction or death (D/AMI). With respect to predetermined values, the authors noted that "C-reactive protein (CRP) levels measured with a high-sensitivity assay are $\leq$1.0 mg/dl in 98% of healthy persons." (Zebrack, p. 145) Table 1 of Zebrack reports that the Median CRP levels for patients presenting with SAP, UAP and AMI are 1.31 mg/dl, 1.27 mg/dl and 2.50 mg/dl, respectively. The authors also noted that for the entire subject population "CRP was a highly significant univariable and multivariable predictor of the composite outcome of D/AMI. For CRP levels above the first tertile (CRP $\geq$1.19 mg/dl), the relative hazard was 1.8 (95% confidence interval [CI] 1.3 to 2.4, p = 0.0002) by univariable analysis and 1.7 (95% CI 1.3 to 2.3, p = 0.0005) by multivariable analysis." (Zebrack, p. 146) This demonstrates that there are predetermined values that are useful in the analysis of disease states.

Another study of CRP levels using a different commercially available high-sensitivity enzyme-linked immunoassay method to assay C-reactive protein (hs-CRP) levels, Auer et al. (Jpn Heart J 2002; 43: 607-619) found that baseline CRP levels in a group of patients with AMI (group

1a; (6.49±2.28 mg/L) were significantly higher than levels in patients with stable CAD (4.35±2.6 mg/L; P=0.02). Auer also reported that levels of CRP in patients with acute myocardial infarction (AMI) or unstable angina (UA) were followed over a 72-hour period: "Within-group comparison showed significant differences over time (Friedman test, P<0.001; [Table II]). The lowest hs-CRP level (5.96±2.26) was observed at baseline and was significantly different from the level after 12, 24, and 72 hours (9.5±9.04; 18.25±11.02; 20.25±10.61; P<0.001)." (Auer, p. 612, see also Table II). Thus the skilled person clearly can assay for levels of proteins that are increased relative to a predetermined value, e.g., a baseline amount.

Comparing the results reported in the Zebrack and Auer articles, one can see that the baseline levels of CRP in AMI, for example, differ by a factor of approximately 4 (2.50 **mg/dl** in Zebrack vs. 6.49 **mg/L** in Auer). Thus, it will be abundantly clear to the skilled person that the predetermined value used in the claimed methods can vary depending on the particular assay used, the condition of the patient (e.g., type of condition, time after onset of symptoms), etc. However, as also is clear in the published literature, persons of skill in the art are accustomed to carrying out such assays with particular predetermined values, or even determining what a predetermined value should be, without any need for undue experimentation.

Thus, it is routine for the person of skill in the art to determine the value of a parameter in a sample and compare this value against a predetermined value for diagnostic purposes. Accordingly, it would not be undue experimentation for the skilled person to practice the invention as it is claimed.

With respect to claim 8 and its dependent claims, Applicant has amended claim 8 to recite that the claim provides a method for monitoring a sample of a patient having or suspected of having cardiovascular condition. Thus the claim no longer requires that a correlation be made between a measured value of Fit-1/ST2 and regression, progression or onset of a cardiovascular condition. The practitioner can monitor the value of Fit-1/ST2 as part of monitoring the health of the patient.

Accordingly, in view of the arguments and claims amendments, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1, 6-8, 10 and 37-48 made under 35 U.S.C. 112, first paragraph.

Rejection Under 35 U.S.C. 112, Second Paragraph

The Examiner rejected claims 8, 10 and 42-48 under 35 U.S.C. 112, second paragraph as incomplete for omitting essential method steps. Applicant has amended claim 8 such that the claimed method is a method for monitoring a sample that does not require correlation of Fit-1/ST2 expression levels with regression, progression or onset of a cardiovascular condition. In view of the Examiner's acknowledgement on page 7 of the Office Action that the skilled person could diagnose cardiovascular disease in cases where Fit-1/ST2 expression levels were increased relative to a predetermined value, Applicant respectfully asserts that the method as now claimed does not omit any essential steps.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 8, 10 and 42-48 made under 35 U.S.C. 112, second paragraph.

Double Patenting

The Examiner provisionally rejected claims 1, 6-8, 10 and 37-48 under the judicially-created doctrine of obviousness-type double patenting over claims 32-37, 46-47, 51-55 and 64-66 of copending application serial number 10/435,482. Applicant respectfully traverses the rejection.

According to MPEP § 804 I. B., if the current claims are otherwise allowable, then the provisional double patenting rejection should be withdrawn. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: October 19, 2006

Respectfully submitted,

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Usefulness of High-Sensitivity C-Reactive Protein in Predicting Long-Term Risk of Death or Acute Myocardial Infarction in Patients With Unstable or Stable Angina Pectoris or Acute Myocardial Infarction

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High-sensitivity C-reactive protein (CRP), proposed as a new coronary risk marker, may reflect either an acute phase reaction or the level of chronic inflammation. Thus, CRP may be less predictive of long-term outcomes when measured after acute myocardial infarction (AMI) than after unstable angina pectoris (UAP) or stable angina pectoris (SAP). A total of 1,360 patients with severe coronary artery disease (≥1 stenosis ≥70%) had CRP levels obtained at angiography. Presenting diagnoses were SAP (n = 599), UAP (n = 442), or AMI (n = 319). During follow-up (mean 2.8 years), death or nonfatal AMI (D/AMI) occurred in 19.5%, 16.1%, and 17.2% (p = NS) with SAP, UAP, and AMI, respectively. Corresponding median CRP levels were 1.31, 1.27, and 2.50 mg/dl (p <0.001). For the overall cohort, increasing age, low ejection fraction, revascularization, and elevated CRP were the strongest of 6 independent predictors for D/AMI. Among those presenting with SAP, CRP levels above the first tertile were associated with an adjusted hazard ratio of 1.8 (95% confidence interval [CI] 1.2 to 2.8, p <0.009) for D/AMI. After UAP, the hazard ratio was 2.7 (95% CI 1.4 to 5.0, p <0.002). However, when measured during hospitalization for AMI, CRP was not predictive of long-term outcome (hazard ratio 1.0 [95 % CI 0.5 to 1.7] p = 0.86). In conclusion, predischarge CRP levels are higher after AMI than after UAP or SAP. However, whereas CRP is strongly predictive of long-term D/AMI for patients presenting with SAP or UAP, it is not predictive shortly after AMI, suggesting that measurements should be delayed until the acute phase reaction is over and levels have returned to baseline. ©2002 by Excerpta Medica, Inc.

(Am J Cardiol 2002;89:145–149)

C-reactive protein (CRP) levels measured with a high-sensitivity assay are <1.0 mg/dl in 98% of healthy persons. Even when relatively elevated within this "normal" range, CRP has been shown to be predictive of a first cardiovascular event in previously healthy men and women.[1,2] CRP also has been reported to be predictive of future events in patients with established coronary artery disease (CAD).[3–5] After acute myocardial infarction (AMI), CRP dramatically increases, peaking in 2 to 4 days and returning to baseline in 3 to 4 weeks.[6] Peak CRP levels are associated with the size of the infarct and are attenuated by early reperfusion.[7] Peak CRP levels after infarction have been associated with the short- but not long-term risk of death.[8] However, the long-term predictive value of CRP measured shortly after AMI is poorly defined.

METHODS

Study objectives and hypotheses: Our objectives were to test (1) whether CRP is equally predictive of long-term clinical outcomes (death [D] or AMI) in patients with angiographically similar CAD presenting with AMI as in those presenting with stable angina pectoris (SAP) or unstable angina pectoris (UAP), and (2) whether the predictive value of CRP overall and in the specific diagnostic subgroups is altered by adjustment for multiple standard risk factors. We postulated that CRP values would be higher after AMI than after SAP or UAP due to an acute phase reaction to tissue injury, but that it would be less predictive of long-term outcome.[9]

Patients: The study sample included consecutive consenting patients at a single hospital undergoing angiography for evaluation of clinically defined SAP, UAP, or AMI. We also selected subjects for the study who survived hospitalization and had angiographically severe CAD, because these subjects had objective evidence confirming the clinical diagnosis of SAP, UAP, or AMI. Of 1,971 patients undergoing angiography with complete demographic data, 1,360

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had severe CAD, defined as ≥1 major vessel with ≥70% diameter stenosis, 187 (9.5%) had mild to moderate CAD, and 424 (21.5%) had a normal coronary angiogram. Of these patients, 1,030 (76%) had an ejection fraction measurement and 881 (65%) had information on discharge medications. Most subjects were residents of Utah, southwestern Idaho, or southeastern Wyoming, a population that is genetically representative of the US Caucasian population. The study was approved by the hospital's institutional review board.

Patients with SAP (n = 599) generally underwent angiography on a short stay (<24 hour or "outpatient") basis. Patients with UAP (n = 442), defined by clinical history and electrocardiographic findings, generally underwent angiography on an inpatient basis. A diagnosis of SAP or UAP was determined from the clinical history by the attending cardiologist, and all such patients had normal creatine kinase-MB levels if drawn. Patients with AMI (n = 319) were defined by clinical presentation and elevation of cardiac markers (primarily creatine kinase-MB), were hospitalized, and underwent angiography before hospital discharge (usually 1 to 2 days after admission). Troponin values were not available in most patients. Long-term (up to 5-year) follow-up for the end point of death was available in 100% of patients; final vital status of those not able to be contacted by telephone was determined through a national death registry.

Determination of CRP: CRP levels were obtained with the use of a fluorescence polarization immunoassay (Abbott Diagnostics, Chicago, Illinois). All serum was analyzed by a high-sensitivity (0.05-mg/dl threshold) protocol with a range of results of ≤0.05 to ≥6.5 mg/dl. Samples with CRP >6.5 mg/dl were reanalyzed by a lower sensitivity protocol (range of results up to 26 mg/dl). The test is standardized to the International Federation of Clinical Chemistry International Reference Preparation for Plasma Proteins.

We prospectively chose to divide CRP values into tertiles for the overall group and for each distinct coronary syndrome subgroup (AMI, UAP, SAP). Because the predictive value of the second and third tertiles compared with the first (defined as reference) was similar, they were defined as "elevated" and combined in subsequent analyses.

Statistical considerations: Baseline demographic and laboratory information is presented as mean ± SD for continuous variables and frequencies for discrete variables and compared among groups by analysis of variance or chi-square testing, respectively.

Survival statistics were used for risk determinations. The primary outcome variable was the combination of death (all-cause) and nonfatal AMI. Only the first event was counted as an end point. Secondary outcome variables were death (alone) or nonfatal AMI (alone). Cox regression analysis was used for assessing the relative hazard of events over time. Both univariable and multivariable analyses were performed using SPSS for Windows, version 9.0.1 (SPSS Inc., Chicago, Illinois). Cox multivariable analyses used a forced entry approach as well as a backward conditional regression approach. Variables were included in final models if adjusted p values were ≤0.10 (2-tailed).

CRP was entered in tertiles for comparison in Kaplan-Meier (log-rank test) and Cox multivariable analyses. (Because the outcomes for the second and third tertiles were not statistically different, they were combined for final analyses.) Seventeen risk factors in addition to CRP were included in multivariate analyses. The first analysis adjusted for traditional risk factors: age, sex, diabetes, smoking history (current or >10 pack-years), a family history of early CAD, a diagnosis of systemic hypertension, a diagnosis of hyperlipidemia, and type of treatment after angiography (medical, angioplasty, or surgery). Additional analyses added additional baseline variables including systolic and diastolic blood pressure, fasting total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, renal insufficiency (creatinine >2 mg/dl), ejection fraction <40%, and number of vessels with severe (≥70%) stenosis.

RESULTS

All patients: Baseline demographics of the 1,360 patients with CAD overall and by diagnostic subgroup are summarized in Table 1. Patients averaged 65 years of age (range 33 to 95), and 77% were men. After AMI, ejection fraction, blood pressure, and lipid levels were lower and CRP higher; however, there were no significant differences among groups in the number of severely stenotic coronary vessels and in D/AMI events.

For the overall cohort, CRP was a highly significant univariable and multivariable predictor of the composite outcome of D/AMI. For CRP levels above the first tertile (CRP ≥1.19 mg/dl), the relative hazard was 1.8 (95% confidence interval [CI] 1.3 to 2.4, p = 0.0002) by univariable analysis and 1.7 (95% CI 1.3 to 2.3, p = 0.0005) by multivariable analysis. Comparing the upper quartile CRP (≥2.25 mg/dl) with the first quartile yielded a hazard ratio of 2.2 (95% CI 1.5 to 3.2, p = 0.0001) by univariable analysis and 2.3 (95% CI 1.5 to 3.3, p <0.0001) by multivariate analysis.

Overall, 47% had interventions (percutaneous intervention, 16%; coronary bypass surgery, 31%) and 53% were treated only medically. There were only modest differences in intervention rates among subgroups (SAP, 38%; UAP, 55%; AMI, 50%), and CRP was similarly predictive overall in those receiving interventions (hazard ratio 1.9) and those treated only medically (hazard ratio 2.0).

CRP above the first tertile was the next strongest predictor of D/AMI after ejection fraction <40% (hazard ratio 2.7, p <0.0001), age (hazard ratio 1.03/year, p <0.0001), and revascularization therapy (hazard ratio 0.7, p = 0.0001) among all variables tested in multivariable analyses. Other independent predictors of D/AMI among all patients were a diagnosis of hyperlipidemia (hazard ratio 0.7 [95% CI 0.6 to 0.9],

TABLE 1 Baseline Demographics

Variable	All (n = 1,360)	SAP (n = 599)	UAP (n = 442)	AMI (n = 319)	p Value
Mean age (yrs)	64.9	66.3*	64.6*	62.7*	<0.001
Male patients	78%	77%	78%	78%	NS
Ejection fraction (%)	60	60*	63*	55*	<0.001
Median CRP (mg/dl)	1.38	1.31	1.27	2.50*	<0.001
Diabetes	18%	16%	22%	17%	NS
Hyperlipidemia	51%	48%	56%*	49%	0.04
Hypertension	54%	57%	56%	52%	NS
Tobacco use (current or>10 pack-years)	27%	22%*	26%*	36%*	<0.001
Family history of CAD	34%	29%*	37%	38%	0.005
Renal failure (creatinine > 2 mg/dl)	5.9%	6.2%	5.4%	6.0%	NS
Systolic BP, mean (mm Hg)	141	145*	142*	131*	<0.001
Diastolic BP, mean (mm Hg)	77	76	77	75*	0.001
Total cholesterol (mg/dl)	181	181	185	176*	0.06
Low-density lipoprotein (mg/dl)	118	119	121	113*	0.04
High-density lipoprotein (mg/dl)	33	32	33	34	NS
Triglycerides (mg/dl)	152	151	158	146	NS
No. of coronary arteries ≥70%	2.0/3	2.0/3	2.0/3	1.9/3	NS
Days of follow-up, mean	1024	1032	1053	969	NS
Death	11.4%	13.0%	9.5%	11.3%	NS
AMI	8.2%	8.4%	7.7%	8.5%	NS
Death or AMI (first event only)	17.9%	19.5%	16.3%	16.9%	NS

*p <0.05 for pairwise comparisons with the other 2 subgroups.
BP = blood pressure; NS = nonsignificant p value (≥0.10).

p = 0.01) and diabetes (hazard ratio 1.5 [95% CI 1.1 to 2.0], p = 0.014).

CRP correlated negatively with ejection fraction, a diagnosis of hyperlipidemia, low-density lipoprotein cholesterol, total cholesterol, and baseline systolic and diastolic blood pressure. However, correlation coefficients were low (≤-0.2).

Stable angina: Among 599 patients with SAP, 117 events of D/AMI occurred (19.5%) (see Table 2). CRP above the first tertile (≥1.15 mg/dl) was associated with an unadjusted hazard ratio of 1.8 (p <0.007) (Figure 1), which was unchanged after adjusting for traditional risk factors. After adjustment for all 17 variables, the hazard ratio increased to 2.3 (p = 0.023); however, the number of subjects with complete data decreased to 285. Age and low ejection fraction were other independent predictors.

Unstable angina: Among the 442 patients with UAP, there were 72 events of D/AMI during follow-up (16.3%) (Table 2). An elevated CRP (≥1.10 mg/dl) was associated with an unadjusted hazard ratio of 2.6 (p <0.002) (Figure 2), which was similar after adjustment for traditional risk factors (2.7). After adjustment for all 17 variables, the hazard ratio increased to 4.2; however, the number of subjects with complete data fell to 219. Low ejection fraction, revascularization, diagnosis of hyperlipidemia, and diabetes were the other independent predictors.

Acute myocardial infarction: During follow-up, 54 events of D/AMI occurred among 319 patients with recent AMI (16.9%) (Table 2). At baseline angiography, median CRP after AMI was 2.50 mg/dl, significantly greater than in the non-AMI groups (1.28 mg/dl, p <0.0001). A CRP above the first tertile (≥1.60 mg/dl) was associated with an unadjusted hazard ratio of 1.0 (p = 0.85), which was unchanged after adjustment for traditional risk factors (Table 2, Figure 3). The hazard ratio was not significantly altered by changing the cutoff for CRP elevation. The hazard ratio for D/AMI increased to 1.6 after complete multivariable adjustments but was still nonsignificant (p = 0.34). Age was the only significant predictor in patients with AMI, but hazard ratios were increased (trends) for low ejection fraction, diabetes, and revascularization, and were similar to those in the non-AMI groups.

Combined non-AMI group (SAP, UAP): Given the similar results in CAD patients without AMI (SAP and UAP), the 2 groups were combined, with CRP ≥1.13 mg/dl defined as elevated above the first tertile. Results are shown in Table 2.

DISCUSSION

Study perspective: In our large CAD cohort with up to 5 years follow-up, we found that CRP was strongly predictive of long-term outcome in patients with SAP and UAP, but not after recent AMI despite higher levels (2.5 vs 1.3 mg/dl). Because the 3 CAD subgroups had comparable angiographic CAD and therapy, we interpret this failure in the AMI group as reflecting a distortion in chronic levels caused by the acute phase reaction associated with myocardial injury. In non-AMI patients, the adjusted relative hazard of elevated CRP was stronger than most traditional risk factors. In contrast, no level of CRP was predictive in the AMI group, although we could not exclude a modest risk association. Similar results were found when those with even mild-moderate disease were included (data not shown).

Long-term event rates in the 3 groups were similar. This also likely relates to similar angiographic CAD severity and intervention rates and to selection of patients with AMI or UAP surviving hospitalization. The inability of discharge diagnosis to distinguish

TABLE 2 Hazard Ratio for CRP Above the First Tertile Among Different Clinical Presentations

	Univariate Analysis	Adjusted for Traditional Risks	Adjusted for All 18 Variables
SAP	n = 599	n = 599	n = 285
Death or AMI	1.8 (1.2–2.8)‡	1.8 (1.2–2.8)‡	2.3 (1.1–4.6)†
Death	3.2 (1.7–6.0)¶	3.0 (1.6–5.7)‖	5.2 (1.5–17.2)‡
AMI	1.2 (0.7–2.3) NS	1.3 (0.7–2.5) NS	1.3 (0.5–3.3) NS
UAP	n = 442	n = 442	n = 219
Death or AMI	2.6 (1.4–4.8)†	2.7 (1.4–5.1)†	4.2 (1.6–11.0)§
Death	2.8 (1.2–6.3)†	2.6 (1.1–5.9)†	2.9 (0.9–9.5)*
AMI	2.3 (1.0–5.2)*	2.6 (1.1–6.2)†	7.3 (1.2–41.7)†
AMI	n = 319	n = 319	n = 162
Death or AMI	1.0 (0.5–1.7) NS	1.0 (0.5–1.7) NS	1.6 (0.6–4.0) NS
Death	0.9 (0.5–1.8) NS	0.8 (0.4–1.6) NS	1.2 (0.3–5.2) NS
AMI	0.9 (0.4–1.9) NS	1.0 (0.5–2.3) NS	2.1 (0.6–9.8) NS
SAP/UAP	n = 1,041	n = 1,041	n = 504
Death or AMI	1.8 (1.3–2.6)¶	1.8 (1.4–3.1)‖	2.5 (1.5–4.2)‖
Death	2.5 (1.5–4.0)¶	2.2 (1.4–3.6)‖	2.7 (1.6–5.5)‖
AMI	1.5 (0.9–2.4)*	1.6 (1.0–2.6)*	2.5 (1.1–5.6)†

*p = 0.050 to 0.10; †p ≤0.05; ‡p ≤0.01; §p ≤0.005; ‖p ≤0.001; ¶p ≤0.0005.
NS = p >0.10.
CRP cutoff is 1.15 mg/dl for SAP (stable angina pectoris), 1.10 mg/dl for UAP (unstable angina pectoris), 1.60 mg/dl for AMI (acute myocardial infarction), and 1.13 mg/dl for the combined SAP/UAP group. Traditional risk factors include: age, sex, systemic hypertension, diagnosis of hyperlipidemia, diabetes, tobacco use currently or >10 pack-years, family history of CAD, and treatment after angiogram (medical, angioplasty, or surgery). Other variables include: baseline cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, systolic blood pressure, diastolic blood pressure, renal failure (creatinine >2 mg/dl), number of vessels with significant stenosis, and ejection fraction <40%.

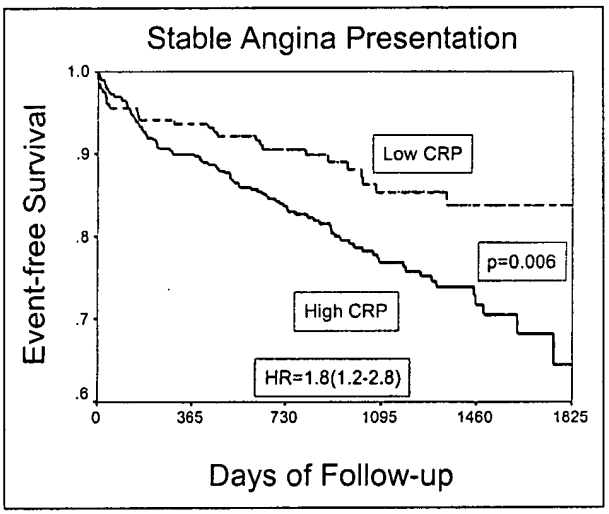

FIGURE 1. Primary outcome events (death or nonfatal AMI) as a function of time of follow-up for stable angina patients with initial CRP above or below the first tertile (1.15 mg/dl). HR = hazard ratio (with 95% CI).

prognosis among groups further highlights the value of CRP.

CRP after AMI (comparisons with published data): CRP levels rise acutely after AMI, reflecting the degree of tissue injury. Peak CRP levels have been reported to predict early post-AMI events, but prognostic utility for later events has been uncertain. Pietila et al[8] evaluated CRP daily after AMI. Peak CRP predicted mortality for up to 6 months, but was not predictive for months 6 through 24. Anzai et al[10] reported that peak CRP levels predicted risk of cardiac death for up to 1 year. Tommasi et al[4] reported that CRP, measured 8 hours after AMI, predicted events at 1 year in 64 patients with normal ejection fraction. None of these studies was sized or designed to address long-term (>6 to 12 month) predictive value of a predischarge CRP after AMI. In patients with acute coronary syndrome, an acute rise in CRP has been reported,[11] but it appears to be restricted to troponin-positive (minor AMI) patients.[12] In the nonacute setting, CRP has been consistently associated with long-term risk for cardiovascular events both in studies of populations at primary risk[1,2,13,14] and in those with established CAD.[3,4,15–19] A meta-analysis supports an independent association of highest tertile CRP (adjusted relative risk 2.1 [95% CI 1.4 to 3.3]).[20]

Considerations in CRP testing: In the absence of injury or infection, the level of CRP in individual subjects is remarkably constant over time, comparable to that of cholesterol.[21] However, the utility of CRP testing may be limited by uncertainties about differences among testing methods,[22] the definition of an elevated CRP, timing after AMI, predictive value in individual patients, and diagnostic and therapeutic implications of an elevated level. In our study, CRP levels in non-AMI patients were higher than some,[3,16,18] but similar to other published reports,[4,10,11,19] including those using the well-known Dade-Behring assay.[17] The definition of elevated CRP in patients with CAD has been extremely variable (range 0.3 to 2.55 mg/dl)[3,4,11,14–19,23,24] but generally higher than cutoff levels used in primary prevention studies (range 0.06 to 0.85 mg/dl).[1,2,25] We defined separate cutoffs for relative CRP elevation based on tertile distributions; a CRP above the first tertile (≥1.13 mg/dl) effectively separated our non-AMI patients (SAP or UAP) into high and low relative risk groups (Figures 1 and 2). However, CRP ≥1.0 mg/dl, often used in published data, was of nearly identical utility. In contrast for the AMI group, no cutoff value rendered the in-hospital CRP measurement informative.

Conclusion: In our group of patients with severe CAD, high-sensitive CRP has strong predictive value for D/AMI in patients presenting with SAP or UAP. CRP is among the strongest predictors of future outcomes along with age, ejection fraction, and revascularization. Although CRP was higher after AMI than for SAP or UAP, it was less predictive (not significant) for long-term events when measured before discharge in these groups with comparable CAD severity. Thus, CRP reflecting chronic inflammation rather

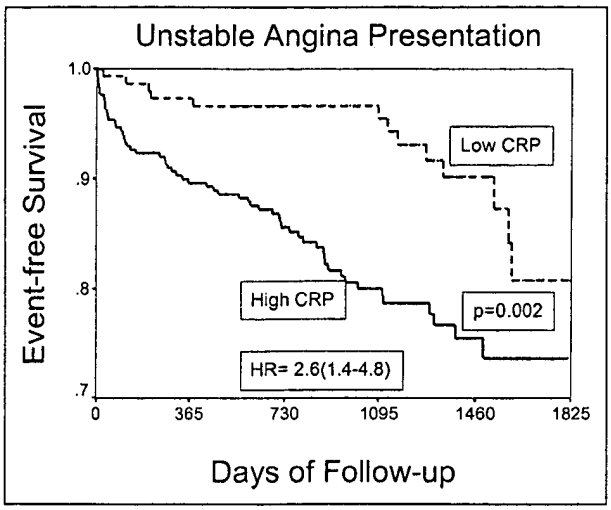

FIGURE 2. Primary outcome events (death or nonfatal AMI) as a function of time of follow-up for unstable angina patients with initial CRP above or below the first tertile (1.10 mg/dl). Abbreviation as in Figure 1.

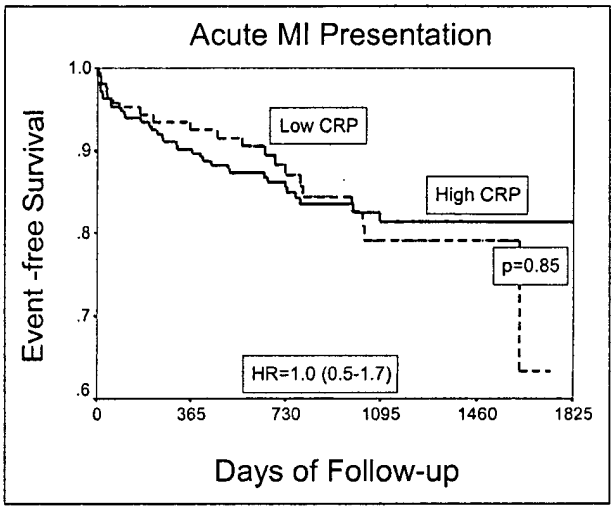

FIGURE 3. Primary outcome events (death or nonfatal AMI) as a function of time of follow-up for patients presenting with acute myocardial infarction (MI) with initial CRP above or below the first tertile (1.60 mg/dl). Abbreviation as in Figure 1.

than relating to an acute phase reaction to injury predicts long-term risk. CRP measurement should be delayed beyond the hospital phase of AMI ($\geq$1 month) when used for chronic cardiovascular risk assessment.

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C-reactive Protein and Coronary Artery Disease

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SUMMARY

Evidence suggests that inflammation plays a key role in the pathogenesis of atherosclerosis. The chronic inflammatory process can develop to an acute clinical event by the induction of plaque rupture and therefore cause acute coronary syndromes.

The aim of this study was to determine the serum levels of the circulating acute-phase reactant C-reactive protein (CRP), which is a sensitive indicator of inflammation, in patients with chronic stable coronary artery disease (CAD) and acute coronary syndromes (ACS).

We studied 56 subjects: 1) 25 consecutive patients (18 men, 7 women; mean age, 68.5±14.3 years, range, 40-86) with unstable angina (UA) or acute myocardial infarction (AMI); 2) 31 consecutive patients (25 men, 6 women; mean age 64±12.7; range, 47-83, years) with signs and symptoms of clinically stable CAD. High-sensitivity-C-reactive protein (hs-CRP) levels were determined with a commercially available enzyme-linked immunoassay method.

In patients with unstable angina and AMI before reperfusion therapy, CRP levels were not significantly different to those in patients with stable CAD (5.96±2.26 versus 4.35±2.6 mg/L; P=0.12), but tended to be higher in patients with unstable angina and AMI. Baseline CRP levels in the subgroup of patients with AMI (6.49±2.28 mg/L) were significantly higher than levels in patients with stable CAD (4.35±2.6 mg/L; P=0.02).

CRP levels in patients with unstable angina and AMI were measured four times during a 72-hour period (0, 12, 24, and 72 hours). The lowest value was observed at baseline and differed significantly from values measured at any other time of the observation period (P<0.001; 5.96±2.26; 9.5±9.04, 18.25±11.02; 20.25±10.61). CRP levels after 12, 24, and 72 hours were also significantly different to the initial values for patients with stable CAD (P<0.01). There was no correlation between CRP and creatine kinase (CK), CK-MB isoenzyme, or troponin I positivity as markers for the extent of the myocardial injury during the observation period.

Baseline levels of serum CRP tended to be higher in patients with unstable angina or AMI but were not significantly different from levels in patients with chronic stable CAD. In the subgroup of patients with AMI, baseline CRP levels were significantly higher than the levels in patients with stable CAD. CRP as a marker of inflammation is significantly increased in patients with AMI and unstable angina shortly after the onset of symptoms (after a period of 12 hours), supporting the hypothesis of an activation of inflammatory

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mechanisms in patients with an acute coronary syndrome or AMI. (Jpn Heart J 2002; 43: 607-619)

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IN patients with unstable angina, persistent or worsening symptoms and signs of ischemia despite full medical therapy indicate a poor prognosis,[1-6] However, at the time of hospital admission, it is not possible to predict whether unstable angina will remit or progress to myocardial infarction, because the causes of instability and the mechanisms underlying its evolution are not known.

The presence of inflammatory infiltrates in unstable coronary plaques suggests that inflammatory processes may contribute to the pathogenesis of these syndromes. In patients with unstable angina, coronary atherosclerotic plaques are characterized by the presence of macrophages, and to a lesser extent, T-lymphocytes, at the immediate site of either plaque rupture or superficial erosion; moreover, the rupture-related inflammatory cells are activated, indicating ongoing inflammation at the site of plaque disruption. These observations are confirmed by clinical studies demonstrating activated circulating neutrophils, lymphocytes and monocytes, and increased concentrations of pro-inflammatory cytokines, such as interleukin (IL)-1 and 6, and of acute phase reactants in patients with unstable angina and myocardial infarction.

A role for inflammation in unstable angina is suggested by histologic studies of unstable coronary plaques,[7-10] evidence of the systemic release of thromboxanes and leukotrienes,[11-13] and the presence of activated circulating leukocytes.[14,15] Furthermore, increased concentrations of plasma C-reactive protein, the prototypal acute-phase reactant, have been reported in some patients with unstable angina,[16,17] in patients with coronary artery disease and other types of angina,[18] and in 20 percent of patients who have an acute myocardial infarction within six hours after the onset of symptoms, before any elevation of myocardial-enzyme levels in serum.[19] The acute-phase reactants are very sensitive, although nonspecific, markers of inflammation. Acute-phase response observed in unstable angina patients may be a primary component of instability because it is not due to myocardial cell necrosis, since it is unrelated to the elevation of troponin,[20] to ischemia because it is normal in patients with severe variant angina,[21] or to activation of the hemostatic system because it does not increase after its activation.[22] The levels may remain elevated for months after waning of the symptoms.[20] In patients with severe unstable angina, elevated plasma levels of C-

reactive protein (CRP) are associated with an unfavorable short-term prognosis.[23]

A long-term predictive value of elevated CRP levels was found in patients with documented coronary artery disease and angina[24,25] and in individuals with multiple risk factors.[26] Moreover, in the Physicians' Health Study, among low-risk individuals, high-sensitivity (hs)-CRP levels within the normal range were linearly related to the incidence of myocardial infarction over a follow-up period of 8 years.[27]

The risk of plaque rupture depends more on the number and activation status of macrophages, the principal inflammatory cells in atherosclerotic plaques, than on plaque size.[28] The mechanisms that relate the level of acute-phase proteins to short- and long-term prognoses in acute coronary syndromes are unclear. The aim of this investigation was to determine whether "active" coronary plaque disruption could be detected by a systemically measureable inflammatory response reflected by CRP levels in unstable angina and acute myocardial infarction. Furthermore, temporal variations in plasma levels of CRP were also examined to investigate whether ischemia-reperfusion injury causes this acute-phase response.

We compared hs-CRP levels in patients with unstable angina (UA)[29] or acute myocardial infarction (AMI) with those in patients with stable coronary artery disease (CAD). A commercially available enzyme-linked immunoassay method was used. Additionally, we examined whether CRP levels increase during UA or AMI, thus serving as a marker for inflammation, and whether this variable is correlated with noninvasive indexes for the extent of myocardial necrosis, that is, creatine kinase (CK), CK-MB isoenzyme (CK-MB), or myocardial troponin I (TnI).[30]

MATERIALS AND METHODS

Patients: We studied 56 patients. Group 1 was comprised of 25 consecutive patients (18 men, 7 women; mean age, 68.5±14.3 years, range, 40-86) admitted to our coronary care unit with unstable angina (UA; n=14) or acute myocardial infarction (AMI; n=11). Inclusion criteria were typical chest pain and either ST-segment elevation ≥0.1 mV in at least two contiguous electrocardiographic leads in patients with AMI and ST-segment depression ≥0.1 mV in at least two contiguous electrocardiographic leads, elevated cardiac tropinin levels, or angina at rest following myocardial infarction within 2 weeks in patients with UA (defined according to Braunwald's classification).[29] In the subgroup of patients with AMI, we excluded patients with the usual thrombolytic contraindications, those with previous myocardial infarction at the same site and those with previous coronary

artery bypass surgery. Patients in group 1 were treated with front loaded recombinant tissue-type plasminogen activator[31] (n=2), percutaneous coronary intervention [PCI] (n=16; coronary stenting in 14 cases), or coronary artery bypass surgery (CABG; n=5). Two (8%) patients were not suitable for coronary revascularisation. Additionally, they received co-medication like aspirin, heparin (low molecular-weight heparin in usual doses or unfractionated heparin according to activated partial thromboplastin time), analgesic drugs, diazepam, nitroglycerin (when systolic blood pressure was ≥90 mmHg) and glycoprotein(GP)-IIb-IIIa-receptor antagonists (n=16) as usual. Blood samples were taken initially after hospital admission (0 hours), and 12, 24, and 72 hours thereafter from a seperate cannula in the forearm. Separation of the serum and analysis were performed immediately.

Group 2 was comprised of 31 consecutive patients (25 men, 6 women; mean age, 64±12.7; range, 47-83 years) with signs and symptoms of clinically stable CAD. Stable angina was defined as typical exertional chest pain relieved by rest, glyceryl trinitrate administration, or both, with positive responses to exercise ECG stress testing, abnormal myocardial perfusion scintigraphy or abnormal stress echocardiography. In all patients symptoms were stable for at least 10 weeks before study entry. None of the patients in this group had experienced a recent (<10 weeks) myocardial infarction, previous PCI, CABG, malignant arrhythmias, cardiac valve disease, apparent acute or chronic liver disease, renal failure, or apparent inflammatory disease. Blood samples were taken after a rest period of 12 hours in the morning before coronary angiography from a seperate cannula in the forearm. Separation and analysis of the serum were performed immediately.

Measurements and methods: Serum CK and CK-MB isoenzyme were measured with an autoanalyzer (Hitachi 917, Roche, Germany) and troponin I was measured by enzyme immunoassay (OPUS, Behring, Marburg, Germany). Values >1.6 ng/mL were considered to be positive.[32] CRP was assayed by rate nephelometry (Behring NA latex CRP; Behring, Germany).[33]

Statistical analysis: Continous variables between groups were analyzed by the unpaired t test or the Mann-Whitney rank sum test where appropriate in case of not normally distributed groups. In case of dichotomous variables, the chi-square test was used. Data within groups were compared with the Friedman test; differences between groups were analysed by the Student-Newman-Keuls test. Correlations were tested by the Spearman rank correlation coefficient,[34] and linear regression analysis was performed. Differences were considered to be significant if the null hypothesis could be rejected with >95% confidence (P values <0.05 [two-tailed] were considered to indicate statistical significance). Results for normally distributed continuous variables are expressed as the mean (± SD) and con-

tinuous variables with non-normal distribution are presented as the median (± interquartile interval).

RESULTS

Comparisons among patient groups: The two patient goups were similar with respect to gender and age (Table I). A box plot graph of hs-CRP values is shown in the Figure. Patients with AMI/UA (after 72 hours) showed the highest CRP

Table I. Characteristics of the Two Patients Groups (Group1 and Group2)

	Group 1 Patients with AMI (n=11) or UAP (n=14)	Group 2 Patients with stable CAD (n=31)
Age (years)	68.5±14.3	64±12.7
Male/female	18/7	25/6
AMI site (anterior/inferior)	7/4	
Delay from onset of symptoms (min)	244±112	
rt-PA/PCI/CABG	2/16/5	
CK-MB (U/L) *	107±84	
Troponin I positive (≥1.6 ng/mL)	18	
(Patients)	(11 [all] with AMI and 7 with UA)	

* Mean ± standard deviation (SD) of the highest individual values. Other values are expressed as mean±SD or number of patients. AMI=acute myocardial infarction; CAD=coronary artery disease; CK-MB=creatine phosphokinase, MB isoenzyme; rt-PA=recombinant tissue-type plasminogen activator.

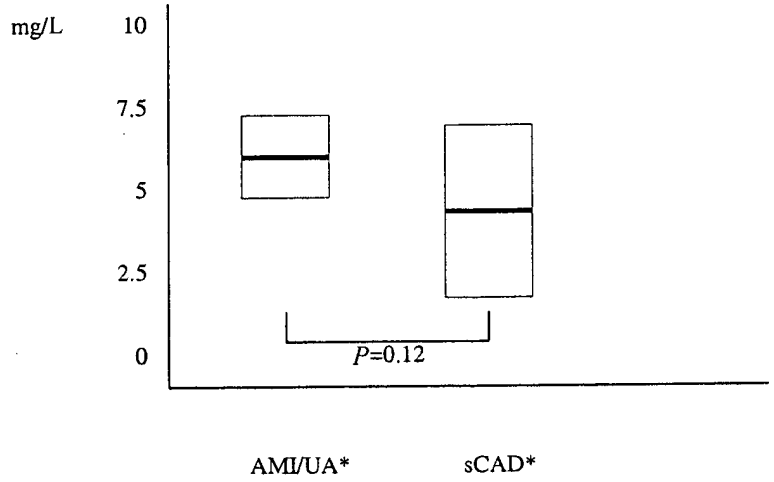

Figure. Box plot graph of baseline hs-CRP values in the two groups (values of patients with AMI/UA are baseline values measured at hospital admission). Values presented are median (center rule in the box) with 25th percentile (lower rule of box), and the 75th percentile (upper rule in box). *AMI=acute myocardial infarction; sCAD=stable coronary artery disease.

levels (20.25±10.61 mg/L; $P<0.001$ versus baseline levels in patients with AMI/UA (5.96±2.26) and $P<0.001$ versus baseline levels in patients with stable CAD (4.35±2.6). No significant difference was observed between baseline values in patients with AMI/UA and patients with stable CAD ($P=0.12$), but hs-CRP values tended to be higher in patients with AMI/UA.

Patients in group 1 were classified into two subgroups: Group 1a comprised 11 patients with AMI (8 men, 3 women; mean age, 65.4±11.2 [range, 40-78]). Group 1b comprised 14 patients (10 men, 4 women; mean age 69.5±15.5 [range, 44-86]) with unstable angina. Patients in subgroup 1a tended (not significant; NS) to have higher baseline hs-CRP values (6.49±2.28) than patients in group 1b (5.47±1.77). Baseline CRP levels in the subgroup of patients with AMI (group 1a; (6.49±2.28 mg/L) were significantly higher than levels in patients with stable CAD (4.35±2.6 mg/L; $P=0.02$).

Smoking status did not differ significantly between the two subgroups (7 smokers and 4 nonsmokers in group 1a, and 9 smokers and 5 nonsmokers in group 1b).

AMI/UA group [group 1]: Patients with AMI or UA were followed up over a 72-hour period. Within-group comparison showed significant differences over time (Friedman test, $P<0.001$; [Table II]). The lowest hs-CRP level (5.96±2.26) was observed at baseline and was significantly different from the level after 12, 24, and 72 hours (9.5±9.04; 18.25±11.02; 20.25±10.61; $P<0.001$). In group 1a patients, no correlation was found between CRP and the duration of symptoms before the first measured CRP values, CK or CK-MB as markers for the extent of myocardial infarction at any time during this observation period (hs-CRP versus duration of symptoms before first measured hs-CRP values, $r=-0.188$, P=NS.; hs-CRP versus maximal CK, $r=-0.243$, P=NS.; hs-CRP versus CK-MB, $r=-0.208$, P=NS). In group 1b patients the hs-CRP values were not significantly different between troponin I (TnI) positive and troponin I (TnI) negative individuals (6.23+2.82 in TnI positive [$n=7$] and 5.84±1.73 in TnI negative patients [$n=7$]; P=NS).

Table II. Time Course of C-reactive Protein (CRP) Levels in 25 Patients with Acute Myocardial Infarction (AMI) or Unstable Angina (UA)

	Baseline	12 h	24 h	72 h	*P* for trend across time
C-reactive protein (mg/L)*	5.96±2.26	9.5±9.04	18.25±11.02	20.25±10.61	<0.01

*Mean ± standard deviation (SD)

DISCUSSION

The results of the present study show that CRP, a marker of inflammation, is significantly increased in patients with AMI or UA shortly after the onset of symptoms. Our data do not demonstrate significantly elevated CRP levels in patients with acute coronary syndromes at baseline compared with patients with chronic coronary artery disease, although CRP levels tended to be higher in patients with AMI/UA.

The results of the present study expand upon previous investigations[17,23] which showed that CRP is raised in patients with AMI and unstable angina shortly after the onset of symptoms compared to patients with stable CAD.

Our data do not support previous reports[17,23,35] which found significantly higher baseline levels of hs-CRP in patients with UA or AMI compared with levels in patients with stable CAD. The present results are consistent with the findings from Berk and colleagues[17] and from Liuzzo and colleagues[23] who reported that baseline hs-CRP concentrations were similar in patients with unstable angina and in those with chronic stable angina, suggesting that hs-CRP levels may be a valid prognostic marker, although it fails to differentiate patients with stable CAD from patients with acute coronary syndromes. A proportion close to 13% of patients with elevated hs-CRP was observed in chronic stable angina patients during the symptom-free periods.

A possible explanation for this finding is that because the affected coronary vessels are small, the total number of activated macrophages involved in unstable coronary plaques is too small to be detected by increased peripheral serum hs-CRP concentrations.

In patients with UA or AMI, the most fatal consequence of plaque rupture, CRP levels changed significantly within 72 hours (Table II). The CRP values shortly after admission to the coronary care unit in patients with UA or AMI were significantly higher than the baseline levels in this patient group and baseline levels in patients with stable CAD. The lowest level was observed at baseline and was significantly different from the levels measured during the following 72 hours. The CRP increase reflects the pronounced activation of inflammation as a cause and a consequence of plaque instability. The CRP increase shortly after admission from AMI/UA observed in our study corresponds with the increase in the white blood cell count[36] and the increase in serum neopterin levels[37] immediately after myocardial infarction. It may also be that the late rise in CRP is partly an indirect consequence of reperfusion or revascularisation therapy.[38]

Our results, together with the evidence of an inflammatory component documented in previous studies,[7-15,17] have important pathophysiologic implications regarding acute-phase response and C-reactive protein levels in patients with

acute coronary syndromes. However, it is not known whether the elevated levels of acute-phase proteins are related to the type of inflammatory stimuli or to the intensity of the individual response.[39] It is also not known whether the stimuli triggering the production of acute-phase proteins arise from the heart[15] or other parts of the body.[14] Ischemia-induced endothelial damage, oxidized low-density lipoprotein,[40] immune complexes, and reactivation of dormant cytomegalovirus or chlamydia infection,[41,42] are all potential causes of vascular injury and an acute-phase response. In addition to their practical clinical importance, the present observations point to new avenues of investigation into the causes of unstable angina and myocardial infarction.

Thus, accumulating evidence suggests that inflammation may cause local endothelial activation, and possibly plaque fissure, leading to unstable angina and infarction. Although no information is yet available on the causes of the inflammation or its localization, these novel lines of research may open the way to a different approach to the patient with acute coronary syndromes. Increased concentrations of hs-CRP, a sensitive marker of inflammation, have been reported in patients with unstable angina.[17,35] It is well known that myocardial necrosis is an established cause of the acute-phase response.[17,23,43] Thus, in addition to plaque rupture, acute phase markers of inflammation may also be elevated because of the presence of necrotic myocardial cells or due to reperfusion injury caused by abrupt closure of the infarct related artery and by initiation of thrombolysis or revascularisation procedure. In patients with AMI, no correlation was found between CRP and the duration of symptoms before the first measured hs-CRP values and CK or CK-MB as markers for the extent of myocardial infarction at any time during this observaton period. Additionally, in patients with unstable angina, CRP values were not significantly different between troponin I (TnI) positive and troponin I (TnI) negative individuals. Therefore, CRP is not a marker for the extent of myocardial damage but indicates inflammation associated with myocardial damage.

In a rat model of myocardial infarction and reperfusion,[44] an early increase in tumor necrosis factor (TNF)-alpha messenger ribonucleic acid (m-RNA) expression in rat hearts with induced myocardial infarction with and without reperfusion has been found. These data support the hypothesis that cytokine gene expression is primarily induced in myocardial cells in response to ischemia. Increased secretion of TNF-alpha in the peripheral blood was found in patients with acute transmural myocardial infarction with a peak of about 24 hours after initiation of reperfusion therapy, reflecting an inflammatory response following ischemia and reperfusion. CRP concentrations in patients with AMI are most probably the result of immune activation related to the atherogenic process, the inflammatory mechanisms that lead to acute coronary events, and the inflamma-

tory response associated with the presence of necrotic myocardial cells in the postischemic or reperfused myocardium. CRP is known to be a marker of stimulation of the cellular immune system.

Plasma levels of CRP start to rise about 6 hours after an acute stimulus, reaching a peak within about 48 hours, and with abrupt cessation of the stimulus, the values then decrease exponentially at a rate close to the measured plasma half-life of CRP of about 19 hours.[45] Thus, after ischemia-reperfusion triggering an acute-phase response, the peak values of CRP are observed after 48 to 72 hours. Our finding, that in the small subgroup of patients with AMI baseline CRP levels were significantly higher than the levels in patients with stable CAD, supports this concept.

The acute-phase response of C-reactive protein is a nonspecific phenomenon reflecting cytokine-mediated hepatic production triggered by most forms of inflammation, infection, and tissue injury. Our patients were carefully selected to eliminate intercurrent disorders likely to be associated with an acute-phase response, and similar attention to intercurrent processes will be essential for the practical application of our findings.

The results of our study confirm the observation that the plasma concentration of C-reactive protein is elevated shortly after admission in the majority of patients with unstable angina, and we also found that C-reactive protein is elevated in the time course after hospital admission in patients with myocardial infarction.

The acute-phase reaction cannot be attributed simply to the disruption of particularly "active" coronary plaques. The magnitude of the acute-phase response is determined to a greater extent by the individual responsiveness than by the type of provocative stimuli.[21]

Experimental studies have shown that periods of ischemia as short as 15 minutes followed by reperfusion elicit a cascade of proinflammatory reactions that include production of oxygen-derived free radicals,[46] activation of the complement system,[47] adherence of neutrophils to the coronary endothelium,[48] leukocyte-mediated injury of the myocardial cells,[49] and production of cytokines,[50] including interleukin (IL)-6 and IL-1, which are the major determinants of acute-phase protein production.[51] In patients, neutrophil activation with signs of endothelial injury and release of proinflammatory cytokines have been demonstrated in acute myocardial infarction[52-55] and after coronary angioplasty.[56] Furthermore, in unstable angina patients a significantly increased urinary concentration of leukotriene E_4 was observed immediately after ischemia compared with 2 days later.[57] Melchiar and colleagues[58] found an increase in urinary neopterin during the first week after myocardial infarction. CRP represents a more practical clini-

cal marker of inflammation than IL-6, the major determinant of their production,[59] because of its much shorter half-life (4 hours).[60]

Our finding that CRP levels increase in patients with AMI/UA shortly after the onset of symptoms supports previous reports, which have shown that acute coronary syndromes are associated with inflammatory mechanisms.[61,62] The results of the present study suggest that Hs-CRP levels fail to differentiate patients with stable CAD from patients with acute coronary syndromes.

Limitations of the Study: Hs-CRP levels may be a valid prognostic marker but fail to differentiate patients with stable CAD from patients with acute coronary syndromes. We did not investigate the prognostic value of hs-CRP measurement in this study.

Hs-CRP levels tended to be higher in patients with AMI/UA compared with patients with stable coronary artery disease. We cannot rule out the possibility that the detected difference could reach statistical significance when much larger patient groups are included in future investigations.

CRP concentrations in patients with AMI are most probably the result of immune activation related to the atherogenic process, the inflammatory mechanisms that lead to acute coronary events, and the inflammatory response associated with the presence of necrotic myocardial cells in the postischemic or reperfused myocardium. The contribution of each of these factors needs to be determined in future trials.

The results of our study should be confirmed by measurements of other sensitive acute-phase reactants, for example serum amyloid A protein. Indeed, serum amyloid A protein may be more useful in routine practice than C-reactive protein, because it has an even wider dynamic range and because most of the commercially available automated assays for C-reactive protein are not sufficiently precise in the low range, as compared with the assay for serum amyloid A protein.

Conclusions: The present data suggest an activation of the inflammatory system in the initial time course in patients with AMI or UA, reflected by increased CRP levels, and extend prior observations concerning acute coronary syndromes to be associated with inflammatory mechanisms.[15,17,61,62] The chronic inflammatory process during the period of stable atherosclerotic disease and in the initial period of plaque instability with only a few inflammatory cells involved, induces CRP production that reaches levels not high enough to detect statistically significant differences in baseline hs-CRP values between patients with stable CAD and acute coronary syndromes. The increase in CRP levels shortly after admission in patients with AMI/UA seems to express the result of immune activation related to the atherogenic process, the inflammatory mechanisms that lead to acute coronary events, and the inflammatory response associated with myocardial injury and myocardial necrosis and reflects an inflammation-mediated process. This

reaction could be affected by other proinflammatory cytokines and possibly by therapeutic interventions. CRP does not represent a marker for the extent of myocardial damage but indicates inflammation associated with myocardial damage.

Baseline hs-CRP may be a valid prognostic marker but is not suitable for distinguishing between patients with stable CAD and patients with acute coronary syndromes. It reflects an activation of the inflammatory system in the initial time course in patients with AMI or UA.

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